Serrano: Hello, you've tuned in to 90.7 FM KALX Berkeley. I'm Karen Serrano and this is “The Graduates” an interview talk show where we speak to UC Berkeley graduate students about their work on campus and beyond. I'm joined today by Brenna Remick from the Department of Molecular and Cellular Biology. Welcome to the show, Brenna.

Remick: Thanks, I’m happy to be here.

Serrano: Yeah. So excited that you're here. Do you want to tell us a little bit about the kind of research you do on campus?

Remick: Sure. Yeah, so I'm finishing up my second year in the Molecular and Cellular Biology program and that's a pretty big broad program that studies a lot of different types of biology. So specifically, I'm in the division of immunology and pathogenesis where we're really interested in studying how the immune system works and how it protects us against infectious disease and also against cancer. So there's a lot of labs studying different aspects of that and I'm in Russell Vance's lab and he is really interested in studying the interactions between our innate immune system and pathogens. So that's what I've been working on for the past year.

Serrano: That's really cool. What kind of Immunology are you working on?

Remick: Yeah, so broadly I'm interested in learning about new ways that our immune system senses the presence of pathogens and I'm particularly interested in the innate immune system. So this is our body's first line of defense against infectious microorganisms and the innate immune system is responsible for sensing the presence of a pathogen and mediating a response that can help restrict or eliminate the pathogen and also plays a role in activating our adaptive immune response and that's mediated by T cells and B cells. So the central idea that's dominated the field of innate immunology for the past few decades has been that we have these sensors that are incurred it encoded in our germline and sensors are called pattern recognition receptors and they recognize these these molecules that are on pathogens called Pathogen-Associated Molecular Patterns. So basically when these receptors bind to these Pathogen-Associated Molecular Patterns, it triggers an immune response, and so this has been the idea for a while now and a lot of the mechanisms have been figured out and we know a lot about how this works. But I'm interested in kind of understanding more about this other arm of the innate immune response that is distinct but complementary to this mode of pathogen sensing and it's something that has been studied a lot in the field of plant immunology for a while but not so much in animals and so I'm interested in studying it how it works in animals. Basically, in this other mode of pathogen recognition rather than recognizing microbial structures the immune system can actually recognize the activities of pathogens. And so when a pathogen infects a cell, it translocates these proteins into the cell that are called effectors and these effectors have a lot of different functions, but mostly they serve to promote infection and will also shut down our host immune responses. So there are certain ways that our immune system can detect the activity of these effector proteins and activate an immune response. And so, like I mentioned it's pretty well established in the field of plant immunology, but a little bit less well understood and

less well studied in the field of animal immunology and so I'm interested in trying to identify new mechanisms by which a human immune system can detect the activity of pathogens.

Serrano: Wow, that's really cool. So from my very limited knowledge of plant immunity… So for plants they recognize, like what you said Pathogen- Associated Molecular Patterns, they recognize cell wall fragments. Is that kind of the same deal in humans?

Remick: Yeah, so similarly they recognize components like the bacterial cell wall or flagellin that's on bacteria and then they can also... there's also sensors that recognize nucleic acids that are delocalized or have modifications that are primarily found on viruses or bacteria nucleic acids, but not in humans. Those are all considered Pathogen- Associated Molecular Patterns.

Serrano: So it's often the case that we know a lot more about the animal side of things and not the plant side of things. So it's kind of interesting to hear that side of things isn't as fleshed out in the animal world. Are you looking at a particular effector protein or particular system?

Remick: So yes, I'm actually doing a screen where I'm focusing on two pathogens, or two viruses. And basically what I'm doing is expressing every gene from this virus individually. I'm expressing each gene in macrophages, a human macrophage cell line, and then I'm looking to see if the presence of that virus protein induces or triggers an immune response in these macrophages.

Serrano: Wow! Every single protein from a virus. It sounds like a lot. How long will that take her? What is the process there?

Remick: So the one of the viruses that I'm working with has 171 genes and the other one, Kaposi's sarcoma-associated herpesvirus, has 89, so it sounds like a lot but it's not it's definitely not anywhere near as many genes as humans have.

Serrano: Oh, absolutely yeah.

Remick: So it's definitely manageable but it is a lot of work because I have to clone each of those genes into a lentiviral vector that I can use to then express in my macrophages. So my macrophages will have the gene that encodes this virus protein and yeah.

Serrano: So you'll have to do that for about 200. Wow, that's a lot. So let's say that one of them does kind of induce a response, what is the plan from there?

Remick: Yeah, so I'm looking at two read-outs of immune activation. The first one is cell death. So if it triggers cell death in the macrophages and the second one is transcriptional immune responses. So I'm looking to see if these proteins might trigger an immune response that's mediated by cytokines and chemokines or maybe an immune related surface molecule. Any of that would be definitely an interest. So then if I get a hit from this then the next steps would be

trying to identify how the host is sensing the virus protein. So what is... what does the pathway look like and basically figuring out the mechanism of how that immune response is initiated.

Serrano: Are there any similar studies like this?

Remick: There has been a few but definitely some more in recent years. So there's been a number of examples of ways that animal immune systems can can detect the activity of pathogens and so one example of this is this protein called NLRP1 that forms something called an inflammasome and inflammasomes can be formed from a number of different proteins that reside in the cytosol and can detect the presence of pathogens. And so when they get activated they form these oligomers and form these high molecular weight complexes and these complexes lead to the activation of downstream proteins that activate inflammatory cytokines and also poke holes in the cell membrane and cause this form of inflammatory cell death called Pyroptosis. And so so yeah, so it had been known for a while that the immune response can get activated by this particular pathogen encoded effector called Lethal Toxin which is encoded by *Bacillus anthracis*, and it was also known that NLRP1 has this auto-proteolytic cleavage site in the protein and this site was was required for its activation. So basically it cleaves itself and then these two proteins are held together. And so this was known, but it wasn't really understood how this protein got activated and what the mechanism was. So what my lab figured out was that this Lethal Toxin cleaves the protein at the N-terminus and that destabilizes the protein and causes it to get degraded by the proteasome. But when the proteasome reaches that auto-proteolytic site where the protein had been cleaved, it stops and so then the other portion of the protein that doesn't get degraded is actually the active part of the protein. So this active part then undergoes more lysis and then activates the downstream proteins that mediate pyroptosis.

Serrano: Wow, that's a great name for a protein that does that! Lethal…. What is it? Lethal Toxin?

Remmick: Yeah. Yeah, so it's cool. And then they also were able to show that another effector from a different pathogen also does a similar thing that leads to the pyroptosis, only a degradation of this N-terminus and activates NLRP1 and since then… So this was done in the mouse NLRP1 protein and since then there's actually been a paper, a couple of papers, showing that human NLRP1 is also activated by pathogen encoded proteins. But this time it's a viral protease so it’s interesting. So it seems that perhaps a major function of this protein was to actually sense the presence of a pathogen protease.

Serrano: Yeah, so you mentioned that you were conducting the screen on I'm guessing like a cell line. Is the plan to move from cells to then like animal studies or what is, kind of, the plan for that?

Remick: Yeah, so it definitely would be interesting to eventually move testing these things into mice. I think it gets kind of complicated because things that we might discover in the human system might not actually be applicable in the mouse system, especially like because of this one

example of NLRP1. We know that the mouse one can recognize certain proteases and the human one recognizes different proteases. But this kind of makes sense because hosts and pathogens are in this arms race all the time. And so these immune sensors are going to be ones that are constantly evolving pretty quickly compared to other proteins. And so maybe less well conserved between animals and between mice and humans for example, right?

Serrano: Yeah, that makes sense. Which two pathogens are you looking at again?

Remick: I'm looking at Myxoma virus, which is a pox virus, that actually only exists in rabbits and doesn't interact with humans..

Serrano: Oh, interesting!

Remick: And then I'm also looking at Kaposi's Sarcoma Herpesvirus and so herpes viruses...It's actually sort of the opposite situation where they've evolved co-evolved with humans for millions of years. So yeah, so we're doing this for a reason actually so viruses they have faster generation times and they have higher mutation rates. And so that means that in this arms race with hosts, they have an advantage because they can evolve more quickly than their host can. Basically if there was a virus and it had an effector protein that activated an immune response, this would be bad for the virus. And so they would want to... basically any mutation that would prevent this immune response from being triggered would be selected for in the virus. And so, so it's possible that in myxoma virus where they're infecting rabbits, this may happen, but since they don't, they're not actually infecting humans that maybe the effector would still be able to trigger an immune response in humans because they don’t have selective pressure to evolve to not trigger that immune response in humans because they don't infect humans. So I think that that's one possibility and then the other possibility is that because humans are never really being infected with myxoma virus, the host might not be evolved to sense the presence of the pathogen. And that's the reason why we're looking at this other virus KSHB that's co-evolved with humans for millions of years because in that case the humans, those that have evolved to sense the presence of the virus would be beneficial to the host and then would be selective for.

Serrano: Right, so then you compare the two responses.

Remick: Yeah, exactly.

Serrano: Nice. So let's say that you do get a hit. Would you then… I know that you have like, you know, hundreds of genes and let's say you end up with like 10 of them that actually do something. Would you then, do you know of any protein domains that are associated with these kinds of proteins and what you should be looking for?

Remick: I'm not sure about specific domains. Do you mean like from the virus or from the host?

Serrano: Yeah from the virus. So like when you, you know, have your list of genes that maybe did something, how could you narrow down your candidates to those that might be worth like the time it takes to actually prove something?

Remick: Yeah, exactly. So a lot of these effector proteins, their functions are kind of known a little bit or at least yeah, what kind of is known is that k there are certain ones that we know shut down immune responses. And so they do various things to the host cell to shut down host replication and promote their own to establish a replicative niche. And so those ones would be kind of a particular interest if we found that they were also being sensed by the host immune response. Oh, yeah. I think that those would probably be the first ones that I would follow up on.

Serrano: Nice! I hope you find something. Is there a certain experiment that you're working on right now?

Remick: Yeah, I am studying mostly these days but I actually just finished the screen and so I'm gonna be getting RNA-seq data back soon. And then I'll be analyzing that. I'm just seeing if anything came of it.

Serrano: Yeah, nice. Has this kind of screen been done before?

Remick: So not to my knowledge. I think there's definitely been a few examples of this like immune responses that are triggered by pathogen activities, but I think most of those were identified not really through a screen but more so just kind of like observations and more like hypothesis-driven research. So I don't think anyone has really, like, systematically looked for this.

Serrano: Nice! So you're doing something brand-new. I was about to ask and I think you kind of just mentioned it, how is like the standard way of doing this? What do people actually do to find these genes if they're not looking at you know, every single gene in the virus?

Remick: Yeah, I think most of the previous examples are just based off of some of the known functions of these pathogens proteins and then just testing a hypothesis and just kind of expressing one of these proteins and seeing if it is, you know can be sensed by the immune system rather than like systematically screening though.

Serrano: Right. I'm sure there are some kind of conserved sets of proteins across pathogens, I may be totally guessing because I know nothing about pathogens, but I guess it was like some proteins had something in common with the rest of the proteins that were in that same category so that you could do like a like a sequence analysis and try to find stuff that is similar?

Remick: I think that yeah, you can definitely do that. I think because pathogens do evolve so rapidly a lot of times it's hard to find sequence-based homology. Okay, but it's definitely possible and then also just because a lot of pathogens do have like these common goals, they often

attack the same host pathways and so even like totally diverse proteins that really have no sequence homology might actually end up doing the same thing.

Serrano: That's a really good point. Yeah, I guess like, how is it that you know humans are able to recognize such totally different types of viruses and react in the exact same way?

Remick: Yeah. So I think that that probably has to do with the other mode of pathogen immunity that I was talking about where a lot of these pathogens have these really conserved microbial features or molecules that can be sensed by the immune system. So for example, if you were looking at Double-stranded DNA viruses, which is like, the two viruses that I'm studying have double stranded DNA in their genomes. A lot of those viruses can be detected by this immune sensor called cGas that recognizes their genomes. So it actually recognizes double stranded DNA and then that initiates an immune response so it is different from effector-triggered immunity. In effector-triggered immunity, I would say it's definitely a little bit more specific to certain pathogens because basically they were sensing the activity of a certain protein and not all pathogens would have that protein but it is definitely possible because as I like kind of was mentioning that a lot of these pathogens are targeting the same host other processes, and so you have an immune system that's guarding a certain host cellular process. So for example, like a lot of pathogens, especially bacterial pathogens, will manipulate the cytoskeleton in cells and so we actually have this immune sensor called prions that guard the cytoskeleton and so if a pathogen perturbs the cytoskeleton this can be sensed by a prion and it triggers effector-triggered immunity and then pyroptosis. Sp by guarding these certain pathways that are commonly targeted by pathogens you can actually sense multiple diverse pathogens with a single sensor.

Serrano: So you mentioned this kind of arms race earlier. Recalling from sophomore year of college evolutionary biology class that there is an arms race, right like the pathogens will evolve in response to... and I've always thought about in like the plant evolving but I guess the human here... how would that happen in effector-triggered immunity because the plant or sorry the human is really guarding, you know a process. So how does the pathogen then evolve beyond that?

Remick: Yeah. So like if the pathogen was triggering some immune response with an effector... If there was a mutation in that viral vector that prevented it from being sensed by the immune system, then that would definitely be selected for here! But I think that, for example, like I was talking about how other proteins sense proteases, these proteases are really important to the virus and are fairly evolutionary fully conserved. And so if they saw a lot of mutations would actually prevent this protease from doing its job and the virus really can't survive. And so that's kind of a good thing from the host perspective because it's limited in its ability to evolve but I will say that in that case what the virus could potentially do is actually have another effector that may be less constrained may evolve to shut down the immune response at a different point so sort of downstream shutting down in immune response. And we see that happening a lot actually and so I think that potentially this is happening a lot and maybe that's why very few examples of this effector triggered immunity have been identified thus far and so I think that

that's also another advantage of the screen I'm doing is that we're expressing individual effectors. So if you have one effector that triggers a response, but then another factor that shuts it off here, we would be able to actually detect that response because we don't have the other protein there to shut it off.

Serrano: Nice. Is it ever the case that it's not just one? I guess you kind of just said this but is ever the case that it is like a group of proteins required to trigger this response? And how does your screen account for that?

Remmick: Yeah. I think that that's definitely possible and that's something that we wouldn't be able to detect in our screen. I can't think of any examples off the top of my head that's already known but I think that that is definitely a possibility.

Serrano: Yeah. So on the host side, is it sort of the same immune response that occurs in response to different pathogens, or is it different or in some kind of way specific to what type of pathogen it is?

Remmick: Yeah. So definitely there could be different host responses depending on the pathogen. So for example viruses can be sensed by interferons as I was talking about. So in addition they also can be sensed by various other host sensors and oftentimes that leads to the induction of this particular immune response called type 1 interferon response. And so what happens there is this infected cell starts making these proteins called interferons which are really potent antiviral proteins and they can signal back on that same infected cell and then also on other cells nearby in the area and then that turns on transcription of a bunch of genes that kind of put the cell in this antiviral state and kind of protects the cell against viruses and then there are also other immune responses. A lot of it is mediated by this particular transcription factor called NFB that is maybe a little bit more appropriate for a bacterial infection, but can initiate responses that can provide defense against bacteria. But, I would say it's not totally black and white like one is for viruses and ones for bacteria, but there's definitely differences.

Serrano: So what is your main hope for this project?

Remmick: Yeah, the most exciting thing would be to discover a new immune sensing pathway. I think that that would be super cool! I don't know if that will happen but I think the major advantage of the approach I'm using is that it's really unbiased and so there's a great potential for discovering something totally novel. That would be really exciting. But for now, I'm just hoping to get any hits so that I have something to work on and have direction to my project. But yeah, we'll see.

Serrano: Have you always been interested in immunology?

Remmick: Definitely for the past two years I would say, but initially when I first started doing research, I was in a cancer biology lab and so I was starting my first introduction to research and then I did a summer internship at Novartis where I worked with cancer T cells and that kind

of got me interested in the field of immunology but it wasn't until I got to Berkeley and started rotating in some labs that I decided that I wanted to study those pathogen interactions and the specifically innate immune system.

Serrano: Where did you go for your undergrad?

Remmick: I went to Cornell.

Serrano: Is that where you did the cancer biology research?

Remmick: Yeah. Yeah. I joined the lab there my sophomore year, the Weiss lab, and then I worked there for three years.

Serrano: You want to talk a little bit about that project? I know it's probably been a while!

Remmick: So I was working on a project that studied this protein called Sirtuin5 and Sirtuin 5 is this protein that is in the mitochondria and it has some roles in metabolism. Basically, it catalyzes post-translational modification of proteins. And so if I had a mutation in this post translational modification, that can affect the activity of other proteins in the mitochondria, and so we were specifically interested in the role of this protein in breast cancer. And so we had the mouse models. These mice would develop breast cancer and we knocked out Sirtuin5 in these mice and then saw that these mice when they didn't have Sirtuin5, they actually had smaller tumors and less metastases in their lungs. So that's just kind of working on trying to figure out why this is happening and what Sirtuin5 was doing that was promoting cancer.

Serrano: Well, that's like a really interesting result!

Remmick: Yeah, there's definitely people in the lab still working on it now and we published a paper a few months ago. So that was pretty awesome.

Serrano: Yeah congrats! Were you always interested in research?

Remmick: I was definitely always interested in science. Like I really liked all my science classes in high school and I thought it was definitely something that I wanted to pursue going forward and I knew that... I had known that kind of doing going to graduate school and pursuing a PhD was definitely an option. I knew that to do that, I would have to see if I liked research first because I knew that that was a big component of going to grad school. So yeah, so I figured I would just give it a try and see if I liked it and it definitely wasn't quite everything I expected. But I definitely really liked it and I liked working through problems and thinking about mechanisms of how things can work. So I definitely enjoyed that and have stuck with it.

Serrano: Nice. So what else are you involved in on campus?

Remmick: So this isn't really through the university, but I am a mentor for 1,000 girls, 1000 futures. So in this program, high school girls from all over the world actually can participate in it and they work through various modules that kind of teach them about science and doing research. So I mentor girls through that and we do like meetings on zoom and just kind of talk about different careers and how they can go about learning more about science and pursuing their interests. So that's so neat.

Serrano: So they're just in high school and this is like maybe an after-school activity for them?

Remmick: Yeah. So so yeah, they're all in high school and they're all girls interested in STEM and it's kind of like a go at your own pace sort of thing. So they basically just have these different modules and they have like a couple months to do each module. And so they can kind of work on it after school or whenever they really have free time.

Serrano: And the modules are teaching them about science careers? Or like more basic science?

Remmick: t's kind of like different components of doing research and it's a little bit less focused on... You're not so much learning facts about science. It's more about establishing good mentor-mentee relationships and thinking critically about things.

Serrano: That's great! That's really important stuff. I wish I had that high school.

Remmick: Yeah. Yeah, it's cool to see these girls who are just like already so excited about science when I feel like I'm definitely inspiring them and I think it will be awesome to see them going forward. Like I know a lot of them are currently applying to college now and so one... I was talking to one girl who was hoping to come to Berkeley actually, which was pretty cool.

Serrano: Yeah. I'm sure that was very rewarding! What do you envision yourself doing after you graduate?

Remmick: I'm definitely not sure yet. Still have a few more years.

Serrano: Right you have so much time!

Remmick: But I do really enjoy teaching and mentoring and so I think I might consider a career in academia. But I also am very open to the idea of working for biotech so we will see.

Serrano: Have you done any teaching so far?

Remmick: Yes. I taught this past fall. I was a GSI for a Molecular Immunology course.

Serrano: Was that during online teaching and how did that go?

Remmick: Oh, yeah, so it was over zoom which was definitely interesting. But I think that it worked out pretty well. I was surprised how much people participated for the most part. Yeah. I thought it was definitely a good experience and I learned a lot from it.

Serrano: That's nice that you got a lot of participation. I feel like, because I also taught that semester, I feel like participation was very low! Was that an upper level course?

Remmick: Yeah. I think that that was probably why because it was mostly Juniors and Seniors and they were definitely all very interested in immunology. And I think of course there's like this extra level of interest given the pandemic and people want to learn about the virus and like our host immune response to it and kind of how vaccines work and I think that that was all super relevant.

Serrano: Wow. Yeah, I didn't even think about that, that you're teaching them immunology during covid.

Remick: Yeah.

Serrano: Yeah, I'm sure you got a lot of questions on that!

Remick: I also am a part of a couple of programs that work with college students who are applying to graduate school and basically just kind of help them through the graduate school application process. And so that was more... I was working on that more in the Fall during the application process and kind of just like reading over statements and looking at resumes and also conducting some mock interviews, that sort of thing.

Serrano: That's fun! Mock interviews.

Remick: Yeah!

Serrano: Great. Well, thanks so much for answering all my questions! So we're getting towards the end of our time here and I'd just like to ask...Is there anything that you'd like to leave the audience with today?

Remick: I guess I would leave the audience with the idea that their immune system is awesome and super powerful and is constantly defending them against tons of infectious agents that are constantly surrounding us and challenging us and our immune system is defending us without us even knowing it and I would also urge everyone to go get their vaccine when it's available to them and to trust the science and know that this is something that virologists and immunologists have have been studying and working on for a long time. And so definitely trust the science and get your vaccine!

Serrano: That's a great message. Yeah, it's like just crazy to think about all the stuff that's happening in your body without you knowing it. So everybody please love their immune systems

today for the rest of the week until our next show! Thanks so much for being on the show with us today, Brenna.

Remick: Thanks for having me.

Serrano: Of course! You've been listening to “The Graduates” an interview talk show where we speak to UC Berkeley graduate students about their work on campus and beyond. We spoke to Brenna Remick today from the Department of Molecular and Cellular Biology. See you next time!